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Left Atrial Function and Ventricular Filling in Hypertensive Patients With Paroxysmal Atrial Fibrillation

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Objectives. We evaluated left atrial dimensions and function, as well as left ventricular structure and filling, in hypertensive patients with paroxysmal atrial fibrillation.

Background. In hypertensive patients, left atrial dilation and enhanced volume transport may facilitate arrhythmias.

Methods. Left ventricular two-dimensional and M-mode echocardiograms and pulsed Doppler echocardiography of transmitral flow were performed in 17 consecutive primary hypertensive patients with paroxysmal atrial fibrillation (group EHf) and in 34 patients with high blood pressure without this arrhythmia (group EH). Seventeen normal subjects (group N) were also investigated. Groups were matched for age and gender.

Results. The EH and EHf groups had similar systolic arterial pressures ([mean ± SD] group EH 185 ± 27, group EHf 173 ± 25 mm Hg, p = NS) and left ventricular mass index (group EH 154 ± 55, group EHf 131 ± 57.8 g/m^2, p = NS), and their M-mode left ventricular systolic wall stress and fractional shortening were comparable to those of normal subjects. M-mode left atrial maximal (group N 37.8 ± 6, group EH 37.9 ± 4.6, group EHf 44.6 ± 6.7 mm, p < 0.05 for group EHf vs. groups N and EH) and minimal diameters and the diameter preceding atrial contraction (group N 31 ± 3.6, group EH 34.5 ± 5, group EHf 40.4 ± 6.9 mm, p < 0.001 for group EHf vs. group N; p < 0.05 for group EHf vs. group EH) were greater in group EHf than in group EH and group N subjects, whereas only the latter diameter was increased in group EH (p < 0.05 vs. group N), so that left atrial fractional shortening was higher than normal only in group EH (group N 10.8 ± 4.4%, group EH 14.6 ± 5.5%, group EHf 9.3 ± 5.3%; group EH vs. group N, p < 0.05; group EHf vs. group EH, p < 0.05). The pulsed Doppler ratio of early to late transmitral flow rates (E and A wave velocity/time integrals × mitral annulus area) was lower than normal in group EH (group N 2.9 ± 2.2, group EH 1.75 ± 0.8, group EHf 2.8 ± 0.8; group EH vs. group N, p < 0.05; group EHf vs. group EH, p <0.001; group EHf vs. group N, p = NS) and was "normalized" in group EHf, early flow being increased in this group (group N 42 ± 13, group EH 39 ± 29, group EHf 60 ± 17 ml; group EHf vs. group N, p < 0.05; group EHf vs. group EH, p < 0.05).

Conclusions. These results suggest that the occurrence of paroxysmal atrial fibrillation in hypertension is associated with enlargement of the left atrium, depression of its contractile function and "normalization" of the pattern of left ventricular filling and is independent of left ventricular hypertrophy and systolic wall stress. The mechanisms linking these variables remain undefined.

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Hypertension may alter the diastolic properties of the left ventricle (1) and disturb the contractile (2,3) and electrical activities of the atrium (4,5), sometimes evolving toward paroxysmal or sustained atrial fibrillation (6,7). Loss of atrial contraction may decrease cardiac output (8) or left ventricular ejection fraction (9). The anatomic and functional atrial and ventricular characteristics associated with the development of atrial fibrillation in human hypertension have not been investigated; the main question of whether the occurrence of atrial fibrillation is associated with distinct patterns of ventricular filling and atrial contractile activity remains unanswered.

We investigated patients with essential hypertension and paroxysmal atrial fibrillation because the latter generally heralds the onset of chronic atrial fibrillation (10), and because a study like this would not be feasible in chronic atrial fibrillation because of the variability of the cardiac cycle (11).

Methods

Hypertensive patients from a group of 280 untreated consecutive subjects admitted to our institute because of high blood pressure were screened for inclusion. Short episodes of paroxysmal atrial fibrillation (lasting from 24 h to 2 weeks and occurring not later than 6 months before admission) had been documented previously in 17 (6%) of them. Thirty-four subjects without any previous episode of atrial arrhythmias were selected from the remaining 263 patients and were matched for age and gender with the patients with the arrhythmia. Seventeen normal subjects of similar age and gender were also investigated. The study was

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approved by the Ethical Committee of our Institute and was illustrated to all subjects involved. Diagnosis of essential arterial hypertension (blood pressure ≥155/≥90 mm Hg) was based on history, physical examination, repeated readings of blood pressure during hospital stay and appropriate diagnostic procedures. Patients with cardiovascular diseases and factors known to be associated with atrial fibrillation (history of smoking, excessive alcohol consumption, diabetes mellitus, hyperthyroidism, rheumatic heart disease) (6,12) were excluded. No episodes of paroxysmal atrial fibrillation had occurred in the 60 days before the echocardiographic study (13); no patient was taking anti-arrhythmic medications or other cardiovascular drugs. Electrocardiogram (ECG) at rest did not show arrhythmias, repolarization or conduction abnormalities, and maximal exercise stress test was negative in all cases.

Echocardiographic study. Echocardiography was performed in a quiet room in the left lateral decubitus position after a 20-min rest. Cross-sectional imaging was obtained from the parasternal and apical windows with an electronic sector scanner (Hewlett Packard, model 77020A) using a 2.5-MHz transducer, followed by a parasternal M-mode recording of the left ventricle and left atrium (14); pulsed Doppler velocimetry of mitral inflow was taken from the ventricular apex (four-chamber view). Sphygmomanometric arterial pressure (as the mean of three consecutive measurements), an ECG and a phonocardiogram were recorded simultaneously. Mitral regurgitation was excluded with color-coded Doppler echocardiography. M-mode and pulsed Doppler tracings were registered at a speed of 100 mm/s on a strip-chart during held expiration, and were coded and digitized off-line in blinded manner by a single observer with the aid of a microcomputer and dedicated software. Three cycles of the M-mode echocardiogram (leading edge to leading edge method) and five cycles of the pulsed Doppler tracings were digitized and averaged. End-diastolic measurements were made coincident with the Q wave of the ECG, and end-systolic measurements (M-mode tracing) were taken at the first high frequency deflection of the second heart sound or at the end of the electrocardiographic T wave (cross-sectional echo).

Cross-sectional imaging. Asymmetric left ventricular hypertrophy, segmental wall dysfunction or mitral valve apparatus alterations was not observed. Maximal (end-systolic, LAAS) and minimal (end-diastolic, LAAD) left atrial areas were measured by planimetry using the apical four-chamber view; transport function of the left atrium was calculated as [(LAAS − LAAD)/LAAS] × 100. Mitral annulus end-systolic (ANNs, cm) and end-diastolic (ANNd, cm) diameters were obtained using the same view from inner edge to inner edge of the basal insertion of the mitral leaflets and were used to quantify diastolic transmitral flow.

M-mode echocardiogram. The following left ventricular variables were calculated: end-diastolic and end-systolic posterolateral wall thickness (PWd and PWs, respectively, cm) and intracavitary diameters (LVDD and LVSD, respectively, cm); end-diastolic septal thickness (IVSd, cm); mass (15) (1.05 × [(LVDD + PWd + IVSd)^3 − LVDD^3] − 13.6 g), indexed to body surface area; fiber fractional shortening ([LVDD − LVSD)/LVDD] × 100); and end-systolic meridional wall stress, as an index of left ventricular afterload (16) (0.98 × [0.334 × SAP × LVSD]/[PWs × ((1 + [[PWs/LVSD]]))] − 2 × 10^3 dynes/cm^2), where SAP (mm Hg) is sphygmomanometric brachial systolic pressure. Left ventricular end-systolic stress/fiber fractional shortening curves were obtained by linear regression analysis and were taken as indexes of the left ventricular inotropic state for each group. Three left atrial anteroposterior diameters were measured (2) (Fig. 1): 1) maximum at ventricular end-systole (LADs, mm), 2) immediately before atrial systole (measured at the end of the ECG P wave) (LADa, mm) and 3) minimum at the end of atrial contraction (measured at the first high frequency deflection of the first heart sound) (LADd, mm). Left atrial fractional shortening was calculated as [(LADa − LADd)/LADa] × 100.

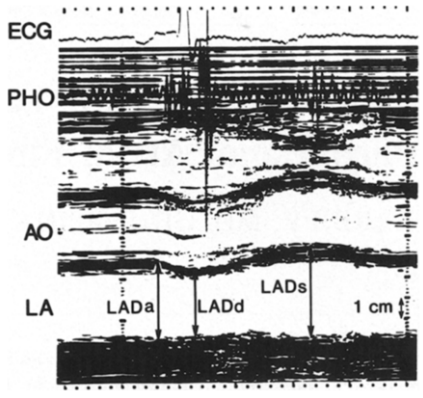

Figure 1. M-mode measurements of left atrial diameters. AO = aortic root; ECG = electrocardiogram; LA = left atrium; LADa = left atrial anteroposterior diameter before atrial contraction; LADd = minimal left atrial anteroposterior diameter at the end of atrial contraction; LADs = maximal left atrial anteroposterior diameter at end-systole; PHO = phonocardiogram.

Doppler echocardiography. The sample volume (length, 4 mm) was located at the mitral valve leaflet tip level (maximal opening in early diastole), with the smallest possible angle (<10°) between the ultrasound beam and presumed direction of blood flow. No angle correction was needed. The following indexes were measured: isovolumic relaxation time (ms), as the time interval between the first high frequency deflection of the second heart sound and the onset of mitral flow in early diastole; peak early and late diastolic velocities (cm/s); Doppler diastolic early/late velocity ratio; deceleration time of early velocity (ms); velocity-time integrals of early and late Doppler velocities (cm); and derived transmitral flow rates in early and late diastole, calculated, respectively, as early velocity-time integral × [(ANNS/2)^2 × 3.14], late velocity-time integral × [(ANND/2)^2 × 3.14] and early/late ratio of transmitral flow. At any heart rate, when deceleration of the early diastolic wave was not linear, the

Table 1. Age, Gender, Hemodynamic and Left Ventricular Ultrasound Data in the Three Groups of Patients

	N (n = 17)	EH (n = 34)	EHf (n = 17)
Gender (male/female)	5/12	17/17	6/11
Age (years)	57 ± 5	60 ± 7	62 ± 9
Heart rate (beats/min)	69 ± 9	72 ± 11	63 ± 9*
Systolic arterial pressure (mm Hg)	127 ± 14	185 ± 27†	173 ± 25†
Diastolic arterial pressure (mm Hg)	78 ± 10	103 ± 11†	108 ± 15†
LV diastolic diameter (cm)	4.7 ± 0.7	5 ± 0.8	4.9 ± 0.5
LV systolic diameter (cm)	2.8 ± 0.5	3 ± 1	2.8 ± 0.4
LV posterior wall thickness (cm)	0.8 ± 0.2	1.2 ± 0.4†	1 ± 0.3
LV septal thickness (cm)	0.9 ± 0.2	1.2 ± 0.3†	1.1 ± 0.2‡
LV mass index (g/m^2)	94 ± 28	154 ± 55†	131 ± 58‡
LV fractional shortening (%)	39.8 ± 6.5	40.2 ± 11	42 ± 8.5
LV end-systolic wall stress (10^3 dynes/cm^2)	50.2 ± 19	69.3 ± 42	57.1 ± 20.6

*p < 0.05 versus the EH group. †p < 0.001 versus normal subjects. ‡p < 0.05. EH = hypertensive patients without atrial arrhythmias; EHf = hypertensive patients with paroxysmal atrial fibrillation; LV = left ventricular; N = normal subjects.

steepest portion of the slope was extrapolated to the baseline.

Statistical analysis. Differences among groups were examined with one-way analysis of variance (Scheffé F test). Linear regression analysis, by the least-square method, was used to test univariate relations between selected variables. For all statistical tests, $p < 0.05$ was considered significant. Data are presented as mean values ± 1 SD; standard error of the estimate (SEE) values are reported in regression analysis equations.

Results

All patients were in the 6th or 7th age decade (Table 1). In hypertensive patients with paroxysmal atrial fibrillation, baseline heart rate was in the normal range, significantly lower than in patients without the arrhythmia (Table 1).

Left ventricular structure and systolic function (Table 1). In hypertensive patients, left ventricular end-systolic meridional wall stress and systolic function were in the normal range. Left ventricular wall thickness and mass index were comparable in both hypertensive groups, and significantly greater than in control subjects. There were no group differences in end-systolic stress/fiber fractional shortening curves (control subjects: $y = 52.4 - 0.27x$, $r = -0.78$, SEE = 3.76, $p < 0.0001$; patients without arrhythmia: $y = 53.3 - 0.22x$, $r = -0.81$, SEE = 4.95, $p < 0.001$; patients with arrhythmia: $y = 56.3 - 0.25x$, $r = -0.61$, SEE = 6.93, $p = 0.009$).

Left atrial dimensions and fractional shortening (Table 2, Fig. 2). Compared with control subjects, only the anteroposterior left atrial diameter before atrial contraction was increased significantly in hypertensive patients without the arrhythmia (Fig. 2, top). In them, left atrial transport function was in the normal range and atrial fractional shortening was increased. In hypertensive patients with the arrhythmia, left atrial cross-sectional end-systolic area and all left atrial M-mode diameters significantly exceeded those in control subjects and in hypertensive patients without the arrhythmia (Fig. 2, top). Although left atrial transport function and fractional shortening were within the normal range, the latter was significantly lower than in hypertensive patients without the arrhythmia (Fig. 2, top). In patients with the arrhythmia no correlation was found between left atrial transport func-

Table 2. M-Mode and Two-Dimensional Echocardiographic Left Atrial Dimensions and Function

	N	EH	EHf
LADs (mm)	37.8 ± 6	37.9 ± 4.6	44.6 ± 6.7*†
LADa (mm)	31 ± 3.6	34.5 ± 5†	40.4 ± 6.9*‡
LADd (mm)	27.6 ± 2.8	29.5 ± 4.9	36.8 ± 7.3*†
Fractional shortening (%)	10.8 ± 4.4	14.6 ± 5.5†	9.3 ± 5.3*
End-systolic area (cm^2)	18.4 ± 28	20.6 ± 5.1	26.1 ± 3.9*‡
End-diastolic area (cm^2)	12.8 ± 2.3	14.9 ± 5.5	17.9 ± 5†
Transport function (%)	29.5 ± 13.2	28.6 ± 11	31.6 ± 15

*p < 0.05 versus the EH group. †p < 0.05. ‡p < 0.001 versus normal subjects. LADa = M-mode left atrial anteroposterior diameter before atrial contraction; LADd = M-mode minimal left atrial anteroposterior diameter at the end of atrial contraction; LADs = M-mode maximal left atrial anteroposterior diameter at end-systole; other abbreviations as in Table 1.

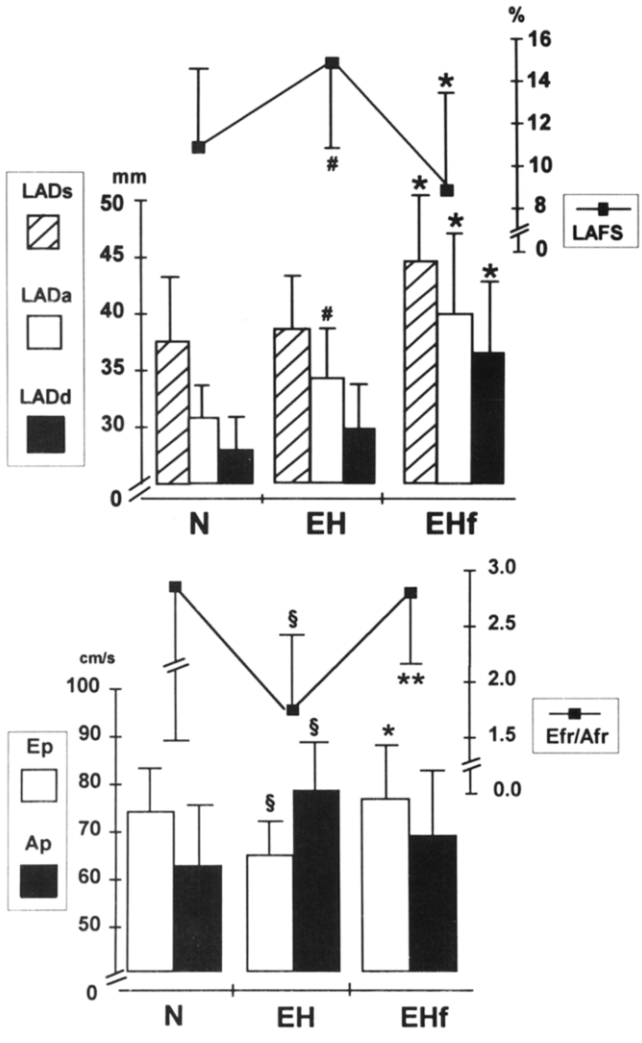

Figure 2. Top, M-mode left atrial diameters and fractional shortening. *$p < 0.05$, hypertensive patients with versus without arrhythmia. #$p < 0.05$, hypertensive patients without arrhythmia versus normal subjects. LAFS = left atrial fractional shortening; EH = hypertensive patients without atrial arrhythmias; EHf = hypertensive patients with paroxysmal atrial fibrillation; N = normal subjects. **Bottom,** Pulsed Doppler peak E and A velocities and E/A ratio of transmitral flow rates. *$p < 0.05$ and **$p < 0.001$, hypertensive patients with versus without arrhythmia. §$p < 0.05$, hypertensive patients without arrhythmia versus normal subjects. Ap = peak velocity of A wave; Ep = peak velocity of E wave; Efr/Afr = ratio of transmitral flow rates; other abbreviations as in Figure 1.

tion or fractional shortening and left ventricular mass or wall thickness, end-systolic wall stress or fractional shortening (for all correlations, $r < 0.4$, p = NS).

Doppler left ventricular filling (Table 3, Fig. 2). In hypertensive patients without the arrhythmia, peak early velocity and early/late ratio of peak velocities and of flow rates were reduced, whereas peak late velocity and flow rate were increased in normotensive subjects. In those with the arrhythmia, peak early velocity and ratio of early to late peak velocities were not different from those of control subjects, but were increased significantly in hypertensive patients without the arrhythmia: early flow rate was significantly greater than in hypertensive patients without the arrhythmia and in control subjects; peak late velocity and flow rate were reduced, but did not attain statistical significance with respect to patients with high blood pressure and without the arrhythmia. The index that best differentiated hypertension with the arrhythmia from that without was the ratio of early to late transmitral flow rate, which was higher in the former group (Fig. 2, bottom). In hypertension with the arrhythmia, a significant correlation was also found between peak early Doppler velocity and left atrial fractional shortening ($r = -0.8$, $p = 0.005$). In all groups, no correlations were found between heart rate and early or late Doppler filling indexes. Isovolumic relaxation time and early wave deceleration time were similar in all patient groups.

Discussion

Atrial fibrillation and hypertension. Two possible links have been proposed between left atrial dimension and atrial fibrillation: 1) that atrial arrhythmia follows atrial dilation as a result of dyshomogeneous conduction of the electrical stimulus (17,18) and 2) that atrial fibrillation causes atrial dilation after loss of effective atrial contraction (19–21). These mechanisms may not be at work in hypertension, especially in the instance of mild atrial dilatation. In this disease, even though the compensatory role of the left atrium to impaired ventricular relaxation (2,3) is well known, the characteristics of left ventricular filling or atrial function have not been related previously to chronic or paroxysmal atrial fibrillation or to left atrial dimensions.

Study methods. Because the frequency of episodes of paroxysmal atrial fibrillation (6,7,22) and Doppler echocardiographic diastolic indexes (23) are related significantly and independently to the patient's age, the groups were matched carefully for age. The time for atrial contraction to normalize after the restoration of sinus rhythm (13,24–29) correlates directly with the duration of the preceding arrhythmic episode (13). Thus, patients who had not experienced recent (within 2 months) or prolonged (>2 weeks) episodes of atrial fibrillation were selected. Left atrial anatomy and function were analyzed with M-mode echocardiograms to have a high temporal resolution for the evaluation of atrial contractility. Atrial diameter modifications evaluated with this technique reflect left atrial volume variations in patients without thoracic deformities, mitral valve disease or markedly dilated left atrium (14).

Left ventricular anatomy and function. Left ventricular eccentric hypertrophy seems to be a stronger precursor of chronic atrial fibrillation than arterial hypertension alone (6,7). Myocardial damage has been suggested to precede the onset of chronic atrial fibrillation (7). Unlike results from previous studies using larger groups of patients with chronic atrial fibrillation (6,7), we were reasonably able to exclude left ventricular systolic dysfunction, decreased inotropic state, increased wall stress or concentric hypertrophy as

Table 3. Pulsed Doppler Left Ventricular Diastolic Filling Variables

	N	EH	EHf
Isovolumic relaxation time (ms)	98 ± 30	95 ± 26	105.2 ± 30
E wave deceleration time (ms)	204 ± 58	216 ± 89	173 ± 54
Peak E wave velocity (cm/s)	74 ± 15	65 ± 14*	77 ± 17†
Peak A wave velocity (cm/s)	63 ± 14	78 ± 22*	69 ± 18
Peak E/A wave velocity ratio	1.2 ± 0.2	0.89 ± 0.3*	1.15 ± 0.3†
Early transmitral flow rate (ml)	42 ± 13	39 ± 29	60 ± 17*†
Late transmitral flow rate (ml)	19 ± 6	27 ± 15*	23 ± 9
Early/late flow rate ratio	2.9 ± 2.2	1.75 ± 0.8*	2.8 ± 0.8‡

*$p < 0.05$ versus normal subjects. †$p < 0.05$. ‡$p < 0.001$ versus the EH group. Abbreviations as in Table 1.

independent factors related to paroxysmal atrial fibrillation. To reconcile these discrepancies, two considerations seem appropriate. Previous studies included patients with cardiomyopathies and left-sided valvular heart diseases, in whom left ventricular and atrial changes are known to be quite variable; because paroxysmal atrial fibrillation generally precedes chronic atrial fibrillation, a lesser degree of left ventricular or atrial involvement may be expected. Therefore, in hypertensive patients other factors might be related to paroxysmal atrial fibrillation and might make a substrate for the establishment of chronic arrhythmia.

Left ventricular filling and left atrial function. Doppler early and late filling indexes were, respectively, depressed and enhanced in our patients without the arrhythmia, as expected (1,3); left atrial diameter before atrial contraction and atrial fractional shortening were increased. Similar observations have been made by Matsuda et al. (3) and Matsuzaki et al. (2) in smaller groups of hypertensive patients, unselected for age. The increased atrial fractional shortening was interpreted as reflecting an atrial Starling effect (increased precontraction atrial diameter secondary to decreased early ventricular filling) or an increased atrial contractility, due to the sympathetic effect or hypertrophy of the atrial wall. Patients with paroxysmal atrial fibrillation showed a peculiar atrial functional alteration and transmitral Doppler flow pattern. In fact, left atrial diameters were greater than in hypertensive patients without the arrhythmia, and atrial contractile function and left ventricular rapid filling, although within the normal range, were, respectively, lower and greater than in patients with high blood pressure without the arrhythmia. These diversities were unrelated to age, left ventricular anatomy, wall stress and systolic function. Heart rate might have accounted partially for these differences (30). However, when patients with similar heart rates were compared, differences in transmitral Doppler velocity patterns were unequivocal. Paroxysmal atrial fibrillation was associated invariably with altered atrial fractional shortening and was unrelated to the time interval from the last episode of arrhythmia.

"Normalized" Doppler mitral inflow. Reduced active atrial emptying leads to increased atrial residual volume at ventricular end-diastole, thus raising the early diastolic atrioventricular pressure gradient and the early ventricular inflow (31,32). Peak early velocity (which in hypertensive patients with the arrhythmia correlated inversely with atrial fractional shortening) is related strongly to the degree of the atrioventricular pressure gradient and left ventricular preload (33,34). The behavior of transmitral flow in the paroxysmal atrial fibrillation group was opposite to that commonly described in the hypertensive heart, and reflected a sort of "normalization" of the ventricular filling. This pattern should be distinguished from that of "pseudo-normalization," which is typical of patients with elevated left ventricular diastolic pressures (ratio of early to late peak velocity is >1 in both conditions) (35) due to excessive atrial afterload impairing atrial fractional shortening (2) and limiting the atrial contribution to transmitral flow. In fact, early deceleration time, which typically is reduced in patients with the "pseudo-normalized" pattern of Doppler transmitral flow (36), was normal in the paroxysmal atrial fibrillation group. Further, normality of left ventricular diameters and systolic function and absence of mitral regurgitation made an elevation of the ventricular diastolic pressure unlikely. Our suggestion is that the occurrence of atrial fibrillation in hypertension is associated with depression of atrial contractility and a distinct pattern of ventricular filling. Although the mechanisms linking these three variables remain essentially undefined, one interpretation may be that patients whose atrial muscle fibers are more susceptible to increased load, wall stress or inotropic stimulation (7) develop atrial tissue alterations facilitating depression of atrial function, "normalization" of the ventricular filling pattern and fragmentation of the electrical impulse conduction.

Conclusions. In hypertensive patients with paroxysmal atrial fibrillation, enlargement and fractional shortening depression of the left atrium are associated with an increased ventricular inflow during early diastole, as a likely mechanism of compensation for the reduced atrial contribution to left ventricular filling. Whether these findings are the cause or consequence of paroxysmal atrial fibrillation remains to be determined.

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